PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	
MARIO CONTORNI	Examiner: Li, Bao Q.
Application No.: 10/593,007	Group Art Unit: 1648
Filing Date: December 2, 2008	Confirmation No.: 6488
Title: COMBINATION VACCINES WITH LOW DOSE OF HIB CONJUGATE	

DECLARATION OF INVENTORSHIP

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mario Contorni, hereby declare as follows:

1. I have reviewed U.S. Patent No 7,348,006 and its corresponding U.S. Patent Publication No. 2005/0158334, entitled "VACCINES COMPRISING ALUMINIUM ADJUVANTS AND HISTIDINE" on which I am a coinventor. I have also reviewed the claims pending in the present application.

2. I understand the Patent Office is relying on U.S. Patent No 7,348,006 and U.S. Patent Publication No. 2005/0158334 in the current Office Action as teaching the claimed invention. I am the original inventor of the subject matter claimed in the above-identified application and of the subject matter disclosed in U.S. Patent No 7,348,006 and U.S. Patent Publication No. 2005/0158334 relied upon by the Patent Office. Massimo Maffiel, listed as a coinventor on U.S. Patent No 7,348,006 and U.S. Patent Publication No. 2005/0158334 and not named as an inventor on the present application, did not conceive of the subject matter claimed in the present application.

3. I declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Sept. 28-2010

Mario Contorni

ADSORBED DIPHTHERIA, TETANUS AND PERTUSSIS VACCINE B.P.

Pasteur Mérieux

Name of Product: Adsorbed diphtheria tetanus and pertussis vaccine BP, Pasteur Mérieux (DTPer/Vac/Ads).

Presentation:

Adsorbed diphtheria, tetanus and pertussis vaccine is a sterile aqueous suspension containing a mixture of purified diphtheria and tetanus toxoids and killed *Bordetella pertussis* organisms adsorbed onto aluminium hydroxide with thiomersal added as preservative. Each 0,5ml dose has a potency of not less than 30IU of diphtheria toxoid, not less than 60IU of tetanus toxoid and not less than 4IU of *Bordetella pertussis* cells.

Indications:

For active immunisation against diphtheria, tetanus and pertussis.

Dosage and Method of AdmInistration:

Adminster by intramuscular or deep subcutaneous injection.

Primary Immunisation:

Three injections each of 0.5ml with an interval of at least 4 weeks between the first and second doses and at least 4 weeks between the second and the third doses. The vaccine may be administered to infants from 2 months of age. If a primary course is interrupted it should be resumed allowing appropriate intervals between the remaining doses.

Reinforcing Doses:

Once primary immunisation is completed, a single reinforcing dose of adsorbed diphtheria and tetanus vaccine may be administered preferably at least 3 years after the last dose of the primary course. Where adsorbed diphtheria and tetanus vaccine has been administered at the start of a primary course, adsorbed diphtheria, tetanus and pertussis vaccine may be administered for subsequent doses. Once three doses of adsorbed diphtheria and tetanus have been administered, monovalent pertussis vaccine may be given at monthly intervals to complete the course. Children presenting for their pre-school diphtheria and tetanus booster who have not previously been immunised against pertussis may be given a single dose of adsorbed diphtheria, tetanus and pertussis vaccine with 2 subsequent doses of monovalent pertussis vaccine given at monthly intervals.

Children aged 10 years and over, Adults and Elderly:

Adsorbed diptheria, tetanus and pertussis vaccine is not recommended for persons aged 10 years or over.

Contra-indications, warnings, etc:

Department of Health Recommendations:

These recommendations are from the 1992 guidelines "Immunisation against Infectious Diseases" (HMSO).

Specialist Advice:

No child should be either immunised or denied immunisation without serious thought as to the consequences, both for the individual child and the community. Where there is any doubt, advice should be sought from a Consultant Paediatrician, Consultant in Public Health Medicine or District (Health Board) Immunisation Co-ordinator.

Alternative Vaccination:

If pertussis vaccine is contraindicated or refused by parents, then DT/Vac/Ads should be offered.

Acute Illness:

If the child is suffering from any acute illness, immunisation should be postponed until the child has recovered. Minor infections without fever or systemic upset are not reasons to postpone immunisation.

Local or general reactions:

Immunisation should not be carried out in children who have a history of severe local or general reaction to a preceding dose. Immunisation should be completed with DT vaccine. The following reactions should be regarded as severe:

Local:

An extensive area of redness and swelling which becomes indurated and involves most of the antero-lateral surface of the thigh or a major part of the circumference of the upper arm.

General:

Fever equal to or more than 39.5C within 48 hours of vaccine; anaphylaxis; bronchospasm; laryngeal oedema; generalised collapse. Prolonged unresponsiveness: prolonged inconsolable or high-pitched screaming for more than 4 hours; convulsions or encephalopathy occurring within 72 hours.

Personal history of epilepsy:

Specialist advice should be sought prior to performing immunisahon on children with a personal history of epilepsy (see above).

Family history of epilepsy:

In a recent British study, children with a family history of epilepsy were immunised with pertussis vaccine without any significant adverse events. These children's developmental progress has been normal. In children with a close family history (first degree relative) of idiopathic epilepsy, there may be a risk of developing a similar condition, irrespective of vaccine. Immunisation is recommended for these children.

Febrile convulsions:

When there is a personal or family history of febrile convulsions, there is an increased risk of these occurring after pertussis immunisation. In such children, immunisation is recommended but advice on the prevention of fever should be given at the time of immunisation.

Evolving neurological disease:

Where there is an ongoing evolving neurological problem, immunisation should be deferred until the condition is stable.

Stable neurological disease:

Stable neurological conditions such as occur in certain patients with cerebral palsy or spina bifida are not a contraindication to immunisation.

Cerebral damage in the neonatal period:

When there has been a documented history of cerebral damage in the neonatal period, immunisation should be carried out unless there is evidence of an evolving neurological abnormality. If immunisation is to be deferred, then this should be stated on the neonatal discharge summary.

Allergy:

A personal or family history of allergy is not a contraindication to immunisation.

HIV:

HIV positive individuals may receive DTP vaccine but pertussis efficacy may be reduced.

Warnings:

Not for intradermal injection.

Side Effects: Pain, tenderness, swelling or redness may occur at the injection site. Generalised reactions may include headache, malaise, pallor, crying, screaming and fever. Attacks of high pitched screaming, limpness and convulsions may occur. More severe neurological conditions including encephalopathy and prolonged convulsions have been reported after pertussis vaccine. Acute allergic reactions may occur, including anaphylaxis, dyspnoea and bronchospasm, urticana and laryngeal oedema. Peripheral neuropathy has been reported. A persistent nodule may occur at the site of injection particularly if the vaccine is administered into superficial layers of the subcutaneous tissue.

Precautions: Although anaphylaxis is rare, facilities for its management should always be available during vaccination.

Use in Pregnancy and Lactation: No reproductive studies have been conducted in animals. There are no data on the use of this vaccine in pregnancy or lactation. The vaccine should not normally be used in pregnancy or during lactation.

Overdose: Not applicable.

Pharmaceutical precautions: Store at +2' to +8'C. Do not freeze. Shake before use.

Legal category: POM.

Package quantities: 0.5ml single dose prefilled syringe (unit pack). 0.5ml single dose ampoule (pack of 5).

Further information: Use of adsorbed diphtheria, tetanus and pertussis vaccine in individuals aged 10 years or over may be associated with severe hypersensitivity reactions. Oral poliomyelitis vaccine may be given simultaneously.

Product Licence No: 6745/0043.

Date of preparation: January 1995.

DTP/0387/1 95/A

UK Product Licence Holder: Pasteur Mérieux MSD Ltd,. Clivemont House, Clivemont Road, Maidenhpad, Berkshire SL6 7BU. Tel:Maidenhead (01628) 785291.

[Vaccination] [Home] [Package inserts]

APPROVED DATA SHEET

TETRAMUNE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed with Haemophilus b Conjugate Vaccine (DTP-HbOC) 0.5 mL and 5.0 mL vials.

PRESENTATION

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate), TETRAMUNE (DTP-HbOC) is a sterile combination of PUROGENATED Diphtheria Toxoid aluminium phosphate-adsorbed, PUROGENATED Tetanus Toxoid aluminium phosphate-adsorbed, Pertussis Vaccine (DTP, TRI-IMMUNOL) and a conjugate of oligosaccharides of the capsular antigen of *Haemophilus influenzae* type b (Haemophilus b) and diphtheria CRM197 protein (HbOC, HibTITER). After shaking, the vaccine is a homogeneous white suspension.

The diphtheria and tetanus toxoids are derived from *Corynebacterium diphtheriae* and *Clostridium tetani,* respectively, which are grown in media according to the method of Mueller and Miller and are detoxified by use of formaldehyde. The toxoids are refined by the Pillemer alcohol fractionation method and are diluted with a solution containing sodium phosphate monobasic, sodium phosphate dibasic, glycine and thiomersal (mercury derivative) as a preservative.

Pertussis Vaccine is prepared by growing Phase I *8ordetella pertussis* in a modified Cohen-Wheeler broth containing acid hydrolysate of casein. The *B. pertussis* is inactivated with thiomersal, harvested and then suspended in a solution containing potassium phosphate monobasic, sodium phosphate dibasic, sodium chloride and thiomersal (mercury derivative) as a preservative.

The oligosaccharides are derived from highly purified capsular polysaccharide, polyribosylribitol phosphate, isolated from *Haemophilus influenzae* type b grown in a chemically defined medium and coupled by reductive amination directly to highly purified CRM197. CRM197 is a nontoxic variant of diphtheria toxin isolated from cultures of *C. diphtheriae* C7 (beta 197) grown in a casamino acids and yeast extract based medium. The conjugate is purified by diafiltration to remove unreacted protein, oligosaccharides and reagents, and sterilised by filtration.

The Haemophilus b conjugate component (HibTITER) is combined with the diphtheria and tetanus toxoids and pertussis vaccine adsorbed to produce the final vaccine. As a preservative, thiomersal (mercury derivative) is added to the combination vaccine to a final concentration of 1:10,000. The aluminium content of the final product does not exceed 0.85 mg per 0.5 mL dose by assay. The residual free formaldehyde content by assay is < 0.02%. Each single dose of 0.5 mL TETRAMUNE is formulated to contain 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid (both toxoids induce not less than 2 units of antitoxin per mL in the guinea pig potency test), 10 ug of purified Haemophilus b saccharide and approximately 25 ug of CRM197 protein. Each 0.5 mL dose of vaccine is formulated to contain less than 16 OPUs of inactivated pertussis cells. The total human immunising dose (the first three 0.5 mL doses given) contains an estimate of 12 units of pertussis vaccine with an estimate of 4

protective units per single human dose. Each component of the vaccine - diphtheria, tetanus, pertussis and Haemophilus b conjugate - meets the required potency standards and contains no other active ingredients.

USES

ACTIONS

Diphtheria is primarily a localised and generalised intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxinogenic strains of *C. diphtheriae.* The highest case fatality rates are in the very young and in the elderly.

Following adequate immunisation with diphtheria toxoid, it is thought that protection lasts for at least 10 years. Antitoxin levels of at least 0.01 antitoxin units/mL are generally regarded as protective. This significantly reduces both the risk of developing diphtheria and the severity of clinical illness. It does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or on the skin.

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *C. tetani.* Spores of *C. tetani* are ubiquitous and there is essentially no natural immunity to tetanus toxin.

Universal primary immunisation with tetanus toxoid with subsequent maintenance of adequate antitoxin levels, by means of timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen and a completed primary series generally induces serum antitoxin levels of at least 0.01 antitoxin units, a level which has been reported to be protective. It is thought that protection persists for at least 10 years.

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis.* This Gram-negative coccobacillus produces a variety of active components including endotoxin and a number of other substances that have been defined primarily on the basis of their biological activity in animals. These active components have been associated with a number of effects, such as lymphocytosis, leucocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, possible neurological effects and adjuvant activity. The roles of each of the different components in either the pathogenesis of, or immunity to, pertussis is not well understood. However, the potency of the pertussis component is measured and shown to be acceptable In the mouse potency test. Serum agglutinin titres have been correlated with protection in clinical trials. The pertussis component induces immunity against pertussis disease in humans.

Most reported illness from *B. pertussis* occurs in infants and young children; two thirds of reported deaths occur in children less than one year old. Older children and adults, in whom classic signs are often absent, may go undiagnosed and serve as reservoirs of disease.

Haemophilus b disease occurs primarily in children under 5 years of age, in which the incidence peaks

between 6 months and 1 year of age. The incidence of invasive Haemophilus b disease is increased in certain children, such as those who are native Americans, black or from lower socioeconomic status and those with medical conditions such as asplenia, sickle-cell disease, malignancies associated with immunosuppression and antibody deficiency syndromes.

The protective activity of antibody to Haemophilus b polysaccharide has been demonstrated by an efficacy study of Haemophilus b polysaccharide PRP vaccine. Data from passive antibody studies indicate that a pre-existinp titre of antibody to PRP of 0.15 ug/mL correlates with protection. A titre of >= 1.0 ug/mL 3 weeks after vaccination is associated with long term protection.

Linkage of Haemophilus b saccharides to a protein such as CRM197 converts the saccharide (HbO) to a T-dependent (HbOC) antigen and results in an enhanced antibody response to the saccharide in young infants that is boostable and predominantly of the IgG class. Laboratory evidence indicates that the native state of the CRM197 protein and the use of oligosaccharides in the formulation of HibTITER Haemophilus b Conjugate Vaccine (HbOC) enhances its immunogenicity. Conjugate vaccines with other carrier proteins will be recognised differently by the immune system. NO DATA ARE AVAILABLE TO SUPPORT THE INTERCHANGEABILITY OF HbOC AND OTHER HAEMOPHILUS b CONJUGATE VACCINES WITH ONE ANOTHER FOR THE PRIMARY SERIES.

HbOC was shown to be effective in a large scale controlled clinical trial. There were no (0) vaccine failures in infants who received 3 doses of HbOC and 12 cases of Haemophilus b disease (6 cases of meningitis) in the control group. The estimate of efficacy is 100% (p = 0.0002); 95% Confidence Intervals (C.l.), 2 tailed, 68%, 100%. Through the end of 1991, with an additional 49,000 person years of follow-up, there were still no cases of *H. influenzae* type b disease in fully vaccinated infants less than 2 years of age. One case of disease has been reported in a 3.5 year old child who did not receive a booster dose as recommended.

TETRAMUNE has been given to 6,793 children as part of a series of studies to test the safety and immunogenicity of this product when compared to separate administration of DTP and HbOC. The vaccines were given at 2, 4 and 6 months of age or at 15-18 months of age.

The antibody response to each of the components of TETRAMUNE was measured (n=189) and compared to separate administration of the DTP and HbOC vaccines (n=189). After three doses, the antibody response to TETRAMUNE was equal to or higher for all four components; tetanus (IU/mL), diphtheria (IU/mL), pertussis (microagglutination) and *H. influenzae* b polysaccharide (ug IgG/mL). In addition, responses to specific pertussis antigens (ie pertussis toxin, FHA and 69K protein) were found to be as high or higher in the TETRAMUNE product compared to separate administration of DTP. Therefore, the immunogenicity of the combined vaccine is at least as good as the two vaccines given separately.

INDICATIONS

TETRAMUNE is indicated for the immunisation of children 6 weeks of age up to the seventh birthday for protection against diphtheria, tetanus, pertussis and Haemophilus b disease when indications for immunisation with DTP vaccine and Haemophilus b conjugate vaccine coincide. Typically, this is at 6 weeks, 3, 5 and 15 months of age and over.

DOSAGE AND ADMINISTRATION

TETRAMUNE is for intramuscular use only.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to

administration whenever solution and container permit.

For infants beginning at 6 weeks of age, the immunisation series for TETRAMUNE consists of 3 doses of 0.5 mL each at approximately 2 month intervals, followed by a fourth dose of 0.5 mL at approximately 15 months of age.

TETRAMUNE may be substituted for DTP and HibTITER administered separately whenever the recommended schedule for use of these two vaccines coincide (see DTP and HibTITER recommended dosage schedules).

DTP; The primary immunising course for infants and children from 6 weeks of age up to their seventh birthday consists of three doses at 4 to 8 week intervals, followed by a fourth dose 6 to 12 months after the third dose. A booster dose is indicated at age 4 to 6 years, preferably prior to entrance into kindergarten or elementary school. However, if the fourth dose was administered after the fourth birthday, a booster prior to school entry is not considered necessary.

HibTITER: infants 6 weeks to 6 months of age should receive three doses at approximately 2 month intervals. Previously unvaccinated infants 7 to 11 months of age should receive two doses approximately 2 months apart. Previously unvaccinated children 12 to 14 months of age should receive one dose. All vaccinated children should receive a single booster dose at 15 months of age or older, but not less than 2 months after the previous dose. Previously unvaccinated children 15 to 60 months of age should receive a single dose of HibTITER. No data are available to support the interchangeability of HibTITER or other Haemophilus b conjugate vaccines with one another. Therefore, it is recommended that the same conjugate vaccine be used throughout each immunisation schedule, consistent with the data supporting licensure of the vaccine.

Preterm infants may be immunised with TETRAMUNE at the usual chronological age from birth.

Simultaneous administration of DTP, HbOC, oral poliovirus vaccine (OPV) and/or measles-mumps-rubella (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Therefore, if there is any doubt whether a vaccine recipient will return for further vaccine doses, TETRAMUNE may be given simultaneously with MMR (at separate sites) and OPV if appropriate for the age and previous vaccination status of the recipient.

Interruption of the recommended schedules with a delay between doses does not interfere with the final immunity achieved; nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.

If a contraindication to the pertussis vaccine component occurs, diphtheria and tetanus toxoids adsorbed (DT) and Haemophilus b conjugate vaccine, HibTITER, should be substituted for each of the remaining doses.

Because this product is a suspension containing an adjuvant, shake vigorously to obtain a uniform suspension prior to withdrawing each dose from the vial. The vaccine should not be used if it cannot be resuspended. The vaccine should be injected intramuscularly. The preferred sites are the anterolateral aspect of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Before injection, the skin at the injection site should be cleansed and prepared with a suitable antiseptic.

Atter insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel.

For either primary or booster immunisation against tetanus and diphtheria of individuals 7 years of age and older, the use of tetanus and diphtheria toxoids adsorbed for adult use (DT) is recommended.

CONTRAINDICATIONS

This product should not be used in individuals 7 years of age or older.

Hypersensitivity to any component of the vaccine, including thiomersal, a mercury derivative, is a contraindication. Immunisation should be deferred during the course of any febrile illness or acute infection. A minor afebrile illness such as a mild upper respiratory infection is not usually reason to defer immunisation.

immunisation with TETRAMUNE is contraindicated it the child has experienced any event following previous

immunisation with a pertussis containing vaccine which is considered to be a contraindication to further doses of pertussis vaccine. These events include:

- · Contraindications and precautions to further DTP vaccination.

  · An immediate anaphylactic reaction.

  · Encephalopathy occurring within 7 days following DTP vaccination.

  · The occurrence of any type of neurological symptoms or signs, including one or more convulsions (seizures) following administration of TETRAMUNE is generally a contraindication to further use. Any decision to administer subsequent doses of a vaccine containing diphtheria, tetanus or pertussis antigens should be delayed until the patient's neurological status is better defined.

  · The presence of any evolving or changing disorder affecting the central nervous system is a

contraindication to administration of a pertussis containing vaccine such as TETRAMUNE regardless of whether the suspected neurological disorder is associated with occurrence of seizure activity of any type.

WARNINGS AND PRECAUTIONS

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered:

- · Temperature of > 40.5degC (105degF) within 48 hours not due to another identifiable cause.
- · Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- · Persistent, inconsolable crying lasting > 3 hours, occurring within 48 hours.
- · Convulsions with or without fever occurring within 3 days.

Although these events are considered to be absolute contraindications, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae.

It is also recognised that in certain circumstances, children with stable central nervous system disorders, including well-controlled seizures or satisfactorily explained single seizures, may receive pertussis vaccine. A family history of seizures is not considered to be a contraindication to pertussis vaccine despite studies indicating that a personal or family history of seizures is associated with increased frequency of seizures following pertussis.

The decision to administer a pertussis containing vaccine to such children must be made by the physician on an individual basis, with consideration of all relevant factors and assessment of potential risks and benefits for that individual. The parent or guardian should be advised of the increased risk involved.

There are no data on whether the prophylactic use of antipyretics can decrease the risk of febrile convulsions.

However, data suggest that the incidence of post-vaccination fever may be reduced by the administration of paracetamol at the time of vaccination and every 4 to 6 hours thereafter to children at higher risk for seizures than the general population.

The clinical judgement of the attending physician should prevail at all times.

If a contraindication to any of the components at this combination vaccine exists, (see CONTRAINDICATIONS) then TETRAMUNE should not be used. For example, if there is a contraindication against the use of a pertussis vaccine component, then diphtheria and tetanus toxoids adsorbed, for paediatric use (DT) and Haemophilus b conjugate vaccine (HibTITER) should be

substituted for each of the remaining doses.

TETRAMUNE should be given with caution to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections (see INTERACTIONS).

As reported with Haemophilus b polysaccharide vaccine, cases of Haemophilus type b disease may occur prior to the onset of the protective effect of this vaccine.

TETRAMUNE will not protect against *H. influenzae* other than type b strains.

Antigenuria has been detected following receipt of Haemophilus b conjugate vaccine and therefore antigen detection may not have diagnostic value in suspected Haemophilus b disease within 2 weeks of immunisation. Routine immunisation should be deferred during an outbreak of poliomyelitis providing the patient has not sustained an injury that increases the risk of tetanus and providing an outbreak of diphtheria, pertussis or Haemophilus type b disease does not occur simultaneously.

Prior to administration of any dose of TETRAMUNE, the parent or guardian should be asked about the personal history, family history and recent health status. The physician should ascertain previous immunisation history, current health status and occurrence of any symptoms and/or signs at an adverse event after previous immunisations in the child to be immunised, in order to determine the existence of any contraindication to immunisation with TETRAMUNE and to allow an assessment of benefits and risks.

Before the injection of any biological, the physician should take all precautions known for the prevention of allergic or any other adverse reactions. This should include: a review of the patient's history regarding possible sensitivity; the ready availability of adrenaline 1:1000 and other appropriate agents used for control of immediate allergic reactions and a knowledge of the recent literature pertaining to use of the biological concerned including the nature of side effects and adverse reactions that may follow its use.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents and cytotoxic agents), a genetic defect, human immunodeficiency virus SHIV) infection or other causes, may have reduced antibody response to active immunisation procedures. Deferral of administration of vaccine may be considered in individuals receiving immunosuppressive therapy. Other groups should receive this vaccine according to the usual recommended schedule. (See INTERACTIONS).

This product is not contraindicated for use in individuals with HIV.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Special care should be taken to prevent injection into a blood vessel.

Full protection against the indicated diseases (tetanus, diphtheria, pertussis and haemophilus type b) is based on a full course of immunisation.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

TETRAMUNE has not been evaluated for its carcinogenic or mutagenic potential or for impairment of fertility.

USE IN PREGNANCY

There is no convincing evidence of risk to the foetus from immunisation of pregnant women, using inactivated virus vaccines, bacterial vaccines or toxoids.

USE IN CHILDREN

The safety and effectiveness of TETRAMUNE in children below the age of 6 weeks have not been established. As with any vaccine, TETRAMUNE may not protect 100% of individuals receiving the vaccine.

Children who have recovered from culture-confirmed pertussis need not receive further doses of a vaccine containing pertussis. However, these children should receive additional doses of diphtheria and tetanus toxoids adsorbed as well as Haemophilus b conjugate vaccine as appropriate to complete the series.

Children who have experienced invasive Haemophilus b disease when < 24 months of age should continue immunisation against Haemophilus b. Children whose disease occurred at >= 24 months need not receive further doses of Haemophilus b conjugate vaccine. However, these children should receive additional doses of OTP as appropriate to complete the series.

ADVERSE EFFECTS

The safety of TETRAMUNE has been evaluated in 6,793 children at 2, 4 and 6 months of age or at 15-18 months of age. The percent of doses administered associated with injection site reactions within 72 hours or common systemic symptoms within 4 days is summarised in Table 1.

Table 1

• ○ ■ ■ ■ ■ ■ ■ ■ % of Doses Assoociated with Symptoms

SYMPTOMS	Infants (542 doses)	Infants [3] (7500 doses)	Toddlers (107 doses)
• Local [1]			
Erythema	34	19	40
Pain/Tenderness	21	30	65
Swelling	20	20	43
Warmth	16		35
• Systemic [2]			
Fever > 38deg C	24	40 [4]	33
Irritability	42	54	49
Drowsiness	26		9
Restless sleep		28	
Loss of Appetite		4	
Vomiting	5	2	
Diarrhoea	9		10
Rash	3		

1 within 72 hours of immunisation

2 within 4 days of immunisation

3 data for this study all collected within 24 hours of immunisation

4 percived fever

As with other aluminium-containinq vaccines, a nodule may occasional be palpable at the injection site for several weeks. Although not seen in studies with TETRAMUNE, sterile abscess formation or subcutaneous atrophy at the injection site may also occur.

The following significant adverse events have occurred following administration of DTP vaccines: persistent, inconsolable crying >= 3 hours (1/100 doses), high-pitched, unusual crying (1/1000 doses), fever >= 40.5degC (1/330 doses), transient shock-like (hypotonic, hyporesponsive) episode (1/1750 doses), convulsions (1/1750 doses).

Although DTP may rarely produce symptoms that some have classified as acute encephalopathy, a causal relation between DTP vaccine and permanent brain damage has not been demonstrated. If the vaccine ever causes brain damage, the occurrence of such an event must be exceedingly rare.

The occurrence of sudden infant death syndrome (SIDS) has been reported following administration of DTP. However, a large case-control study in the U.S. revealed no causal relationship between receipt of DTP vaccine and SIDS. A recent study in Northern California found no increase in the rate of SIDS among TETRAMUNE recipients.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT although it has been shown that there is no causal relationship to the administration of preparations containing diphtheria, tetanus and/or pertussis antigens. The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of vaccines containing DTP.

Bulging fontanelles has been reported after DTP immunisation, although no cause and effect relationship has been established.

Cardiac effects and respiratory difficulties, including apnoea have been reported rarely following DTP immunisation.

Other events that have been reported following administration of vaccines containing diphtheria, tetanus, pertussis or Haemophilus b antigens include: urticaria, erythema multiforme or other rashes and arthralgias. More rarely, a severe anaphylactic reaction (eg urticaria with swelling of the mouth, difficulty breathing, hypotension or shock) and neurological complications, such as convulsions, encephalopathy and various mono- and polyneuropathies, including Guillain-Barre syndrome have been reported.

INTERACTIONS

Children receiving immunosuppressive therapy may have a reduced response to active immunisation procedures.

As with other intramuscular injections, TETRAMUNE should be given with caution to children on anticoagulant therapy.

Tetanus Immune Globulin or Diphtheria Antitoxin, it used, should be given in a separate site with a separate needle and syringe.

It is recommended that influenza virus vaccine should not be administered within 3 days of immunisation with a pertussis containing vaccine since both vaccines may cause febrile reactions in young children.

No impairment of the antibody response to the individual antigens was demonstrated when HibTITER was given at the same time, but at separate sites, as DTP plus Oral Polio Vaccine (OPV) to children 2-20 months of age or Measles, Mumps and Rubella Vaccine (MMR) to children 15 months of age.

No data is available on the concomitant usage with Hepatitis B vaccines.

PHARMACEUTICAL PRECAUTIONS

Store refrigerated away from freezer at 2-8degC.

DO NOT FREEZE.

Multidose vial should be discarded one month after the first dose has been removed.

MEDICINE CLASSIFICATION Prescription Medicine

PACKAGE QUANTITIES

0.5 mL vial (single dose) as single vial or 10 vial pack sizes 5.0 mL vial (10 doses)

FURTHER INFORMATION

Nil

NAME AND ADDRESS

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